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Annual Report No. 4

Solid State Biology, Cellular Water Structure, and Ion Complexing with Application to Navy Medicine

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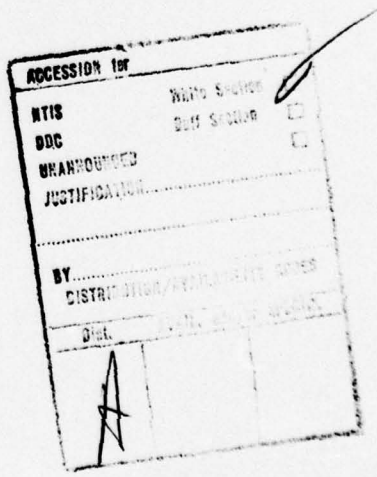
Abstract

This project is intended to provide improved understanding of salt and water metabolism and of solid state physical electron transport in cells, in order to improve medical treatment of shock and of other salt and water disease problems, to facilitate the use of electromagnetic fields in healing and to understand their harmful effects. Comprehensive yet elementary summaries of the recent revolution in salt and water biophysics have been written and are attached (Appendices A and B). The Weber-Fechner law of physiological and psychological response to stimuli is shown to be a consequence of structured water and associated cations in cells. Nerve conduction and muscle contraction are suggested to involve cooperative interactions of the cation association site and structured water system. Electron interactions with structured water leading to superconduction in living systems are shown to be a possible mechanism for non-thermal effects of microwaves on biological systems.



The work of this project is intended to provide improved understanding of salt and water metabolism and of solid state physical electron transport properties of cells, as foundations for improvements in medical treatments of shock and other disturbances of tissue salt and water, and for improvements in electromagnetic methods of facilitation of healing of bone fractures and regeneration of amputated limbs.

The revolution in salt and water biophysics, of which this project is a part, after smoldering quietly for 25 years has now flamed forth into view of the scientific public with news articles and letters in Science (Science, 192, 1218-1222, 1976; 193, 528-530, 608-609, 1976). Therefore, two elementary but comprehensive summaries, one scientific, and one historical (past, present, and future), written by a participant (the present author) for those who would like to know what has and is likely to happen, are included with this report (Appendices A and B). This new knowledge makes necessary major changes in theories of ion and water transport, of excitability, and can provide a foundation for new medical treatments of disturbances of salt and water metabolism in stress and disease states. These summaries will be published soon in the open literature.

In past years, under this project, we have concentrated on obtaining experimental evidence, mostly by nuclear magnetic resonance (NMR), for water structuring and cation association in cells. These are now adequately proven both by NMR, and by other techniques, especially those developed by Ling and Troshin (see Appendices A and B). We have therefore turned to the study of structured water and associated cations in

integrated physiological processes and of interactions of structured water with the electron transport processes in the solid components of the cell, which may involve superconduction and switching processes in cells, and the effects of enviromental electromagnetic fields on cells. It also seems likely that electron-water interactions may provide the bridge between the two presently unreconciled approaches to the mechanism of potassium-sodium selectivity of the cell - namely the association - induction hypothesis of Ling and the cytotonus, water restriction hypothesis of Damadian.

With regard to application of structured water and associated cation concepts to integrated physiological processes, we have proceeded as follows: We had shown previously that sodium and potassium leakage from cells under non-equilibrium conditions can be described by the Elovich equation, which is predictable from the hypotheses of structured cell water and associated cell sodium and potassium, which implied that cell ion conduction obeys solid state physical laws (1,2). We have now been able to show that the above fact leads to the expectation that cellular response to any stimulation which disturbs the ionic equilibrium may be expected to follow the Weber-Fechner law (response is proportional to the logarithm of the stimulus) (3). The Weber-Fechner law has been observed empirically for many years for tissue and organism responses to many types of stimuli (visual, auditory, tactile). It is now evident that this observed behavior of tissues and organisms is a logical consequence of the concept that cell water is structured and cell cations are associated.

The work of Ling has indicated that equilibrium concentrations of cations in cells can be calculated from theory based on the hypothesis of cooperative interactions between sites which bind sodium and potassium. Under the present project, we have extended the above concept to non-equilibrium situations, and have concluded that the kinetics of change of various transient events in organized biological systems probably are governed by cooperative interactions and phase transitions, not by classical mass action kinetics of colliding molecules in free solution as usually supposed (4). Examples of systems in which cooperative interactions probably govern kinetics of change seem to be tension in the tetanically stimulated muscle, potassium conductivity in the depolarized squid axon, and the flash of the living firefly (4). For the case of the firefly, measurements of the light flash of the intact living system made under the present project showed kinetics very different from those obtained in the test tube with the purified firefly enzymes, showing that supramolecular factors, present in the intact cell but not in free solution, governed reaction rate (5).

Solid state electron interactions with structured cell water have been given study in this project during the past year. Studies by Ling, together with NMR studies of cell water by Cope under the present project and by Hazlewood and Damadian, have shown clearly that the macromolecules of the cell influence the behavior of cell water by increasing its structure. There are however suggestions in the literature of the inverse process also, i.e., the presence of water, and conceivably its structuring, may influence the behavior of the macromolecules and

solids in the cell. For example, Rosenberg has shown that the degree of hydration influences the semiconduction activation energy of proteins. McGiness has shown that electrical switching behavior of melanin is dependent upon the degree of hydration. Under this project, we have confirmed the finding of McGiness. Wolf has observed superconduction in the bile acids at temperatures almost as high as physiological temperatures, and has observed that water plays a role in this process. Evidence for superconduction in a wet protein has been obtained by others. In work on the present project, it was noted that superconductive junctions can be made into highly sensitive microwave detectors, and it was therefore pointed out that the probable existance of superconduction in components of living systems provides a possible mechanism for non-thermal biological effects of microwaves (6).

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Appendix A

Structured Water and Associated Cations in Cells,

A Brief Review of the Big Picture.

by

Freeman W. Cope

Two opposing concepts of cell salt and water biophysics now exist. Only the old one is usually discussed. I will here describe the new one and will emphasize that cell water structuring and cation association are not seperate hypotheses, but are two parts of a single integrated concept. The new concept implies that drastic revisions are necessary in old theories of ion and water transport, of excitability, and of salt and water disturbances in disease. Interpretations and directions of experiments, and avenues for application to medical diagnosis and therapy, have become entirely different than before.

In the past, the cell was hypothesized to be a membranous bag containing liquid water in which cations were in free solution. The newer concept is that the cell is like an ion exchange granule, with structured water in the interstices, and with Na^+ and K^+ associated with fixed negative charges on the macromolecules.

The old hypothesis was chosen in earlier times because it was the simplest which was consistent with the available early data. Later, Na^+ and K^+ pumps had to be hypothesized to account for the maintenance of differences in Na^+ and K^+ concentrations across the cell surface in the face of observed leakages of these ions across the cell surface. Despite great effort, no working pumps have been isolated from the cell. Na-K-ATPases have been isolated, but no connection of these with pumps has been proven.

The difficulty with pumps is that the cell does not provide enough energy to operate them. The metabolic systems of muscle can be poisoned so that almost no ATP is produced, yet cell cation concentrations and transmembrane cation leakage rates remain constant for hours. Hence, the hypothetical cation pumps must still be in operation. Under these conditions, Ling[1,2] showed that the energy available to operate the hypothetical pumps is grossly inadequate. The same inadequacy of energy production compared with the needs of the hypothetical pumps was demonstrated by Damadian[3,5] in E. Coli deprived of glucose. Therefore, it is necessary to discard either the law of conservation of energy or the cation pumps. The easier alternative is to discard the pumps, which are not necessary and have never been isolated. One must, however, also discard the entire old cell salt and water picture.

What is the alternative picture? We regard the cell as an ion exchange granule with negatively charged sites with which Na^+ and K^+ associate. The sites markedly prefer to associate with K^+, which is what maintains the observed high intracellular concentration of K^+. In the interstices of the cell ion exchange granule, the water is structured (not as much as ice but more than liquid water), so that cation solubility is low. Na^+ solubility in cell water is therefore low, and little Na^+ is associated with charged sites because of their preference for K^+, so that total cell Na^+ concentration is low, as observed. As with an ion exchange resin, cations in the cell exchange freely from association sites to water. Thus cation concentration

gradients are maintained and cation exchange occurs, without cation pumps and without energy consumption, which is consistent with the findings of Ling[1,2] and of Damadian[3-5] that the cell does not produce enough energy to operate cation pumps.

With the new picture, all the old theoretical approaches based on dilute solutions, pumps, and channels are wrong, and must be replaced by approaches based on physical-chemical reality. Three approaches have been used, which overlap and are probably partly equivalent. They are the statistical mechanical approach (the association-induction hypothesis) of Ling[2,18], the ion exchanger resin theory of Damadian[22,24], and the solid state physical approach of Cope[25-28].

The experimental evidence for the new picture is overwhelming, and includes four main lines of study: (A) equilibrium concentration dependences of intracellular vs extracellular solute concentrations, which indicate water structuring and solute association with macromolecules[29,30], (B) thermodynamic impossibility of cation pumps, (C) nuclear magnetic resonance (NMR) evidence for structured water and association of Na^+ and K^+ with macromolecules, and (D) slow diffusion of H^+ and K^+ in cells indicating structured water.

The new picture leads immediately and obviously to predictions regarding the NMR behavior of H_2O, Na^+ and K^+. Short NMR relaxation times of H and D expected for structured cell water are observed [6-11] and short NMR relaxation times expected for cell Na^+ and K^+ approaching

those observed for Na^+ and K^+ on ion exchange resins are also observed[12-15]. Proponents of the old picture have generated complex, additional, unproven hypotheses to try to make the NMR observations consistent with the classical hypothesis. These intellectual exercises are unnecessary, because all NMR findings are the obvious expectations based on the modern concept.

Kushmerick and Podolsky[16] measured diffusion of cations along a single muscle fiber with results as expected for the classical picture of no ion association and no water structuring. Later Ling and Ochsenfeld[17] showed that if the muscle is handled with sufficient care, the results are entirely different, and cations diffuse as if associated and in structured water. Hence, when cation diffusion in muscle is measured without damaging the muscle fiber, the results support the modern picture. Kushmerick and Podolsky[16] worked with damaged dead muscle fiber, which had lost its ion association and water structuring properties.

The above described the cell at rest. During excitation, configurational changes of cell proteins occur, causing changes of Na^+ vs. K^+ association preference and of water structuring[18]. Energy in the form of ATP is needed to reestablish the resting state[18]. The development of a detailed understanding of excitability in terms of the new picture, to replace Hodgkin-Huxley theory, has only just begun.

A practical result of the new picture of cell salt and water is the development by Damadian[19-21,31,32] of an NMR method of cancer diagnosis based on differences in NMR relaxation times of H in cell water between cancer and normal tissues. The old concept of cell salt and water has led to no useful results to the best of my knowledge.

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Appendix B

Structured Water and Associated Cations in Cells.

Historical Notes, Present Status, and Future Directions.

by

Freeman W. Cope

Many suggestions and various indirect evidence for structured cell water are to be found in the older literature.[1-5]

Some historical notes on the old membrane theory of the cell have been provided by Ling.[6,7]

Modern history of the salt and water revolution begins with Gilbert Ling, who invented the intracellular microelectrode while a graduate student at the University of Chicago in 1948, but then concluded that the concepts of salt and water biophysics for the study of which he had invented his electrode were full of contradictions and must be totally wrong. Ling[8] then developed a new picture of the cell, including the concepts that cell water was structured, that cell cations were mostly associated with macromolecules, and that cation pumps did not exist. In 1949, Ling[9] showed that cation pumps were thermodynamically impossible. Because he was in total disagreement with those in power in the scientific community, Ling was mostly prevented from publishing his new concepts and experimental work in scientific journals. His publication was therefore mostly delayed until 1960, when his collected studies were published as a book.[10]

Modern salt and water biophysics had a simultaneous and independent beginning in Russia at the Institute of Cytology in Leningrad with Nasonov, who initiated the development of concepts analogous to those of Ling, which he summarized in a book, which has been translated into english.[11]

The russian research and that of Ling[12,30,36] proceeded along independent but parallel paths as Troshin and Ling both studied the equilibrium concentrations of various electrolytes and non-electrolytes inside vs outside of cells, and both showed that most solutes followed modified Langmuir binding isotherms, which implied one fraction of solute associated with macromolecules plus a second fraction dissolved in structured intracellular water. Troshin's work was summarized in a book, which has been translated into english.[13]

By 1970, by the intelligent use of classical methods of analysis, the evidence for structured cell water and associated cations in cells had become very strong.

Beginning in 1965, nuclear magnetic resonance (NMR) provided much confirmation and some extension of the evidence from classical methods. In regard to cell water structuring, Bratton et al[14] in 1965 first measured by pulsed NMR the short relaxation times of hydrogen of muscle water compared with liquid water, which have been confirmed repeatedly. In regard to cation association, Cope[15-17] in 1965 first performed NMR analysis of ^{23}Na in tissues and showed that ^{23}Na in cells behaves like Na^+ associated with charged sites on an ion exchange resin, not like Na^+ in free solution. Unlike the work of Bratton et al[14], the NMR measurements of Na^+ by Cope[15-17] were intended specifically to test the concepts of Ling, and were initiated because solid state physical concepts of electron transport in

cells developed by Cope[18,19] showed analogies with cation transport in cells, which only could be valid if Ling's concepts of cation association were valid.[20,21]

An explosion of NMR studies began in 1969 as Hazlewood et al[22] and Cope[23] independently, but at the same time using different NMR techniques, both showed an approximate 80 - 20 percent split of cell water into two fractions, both with more structure than liquid water. The NMR explosion continued as Cope and Damadian[24-27] demonstrated that ^{39}K in cells behaves like K^+ associated with an ion exchange resin, not like K^+ in free solution, and with the discovery by Damadian,[28,29] and confirmation by many others, that the NMR relaxation time of cell H_2O can be used for diagnosis of cancer.

The thermodynamic impossibility of cation pumps in the cell was given further evidence in muscle by Ling[30] and in bacteria by Minkoff and Damadian.[31]

Conceptual advances occurred as Damadian[32-34] pointed out multiple analogies of the salt and water behavior of the cell to that of an ion exchanger resin granule. This led to the discovery by Minkoff and Damadian[35] of a probable contractile protein in bacteria which is necessary for K^+ accumulation, which led to the concept that the experimentally observed preference of cell association sites for K^+ over Na^+ is controlled by restriction of concentration of intracellular water due to extrusion of water from the cell by shortening

of the contractile fibers of the cell (termed cytotonus by Damadian[35]).

The status of the new picture of cell salt and water biophysics at the present moment in its history seems to be (as of September 1976):

1. The evidence is overwhelming for structured cell water, for associated Na^+ and K^+ in cells, and for the absence of cation pumps. One should regard the cell as an ion exchanger resin granule, whose association sites on proteins have a marked preference for K^+ over Na^+. During excitation, this preference is reduced by a configurational change of the proteins, but is re-established by ATP which restores the resting state configuration of the proteins.

2. More work to prove structured water and associated cations in cells is <u>not</u> needed because these are adequately proven. The selectivity of association sites for K^+ over Na^+ is well demonstrated.[12,30,36-38] The important question now is the physical mechanism by which this selectivity is established. The two possible mechanisms which have been proposed are electron displacements within the protein (association-induction hypothesis) of Ling[10,30] or cell water restriction by cytotonus advocated by Damadian.[35] The solution of this question of mechanisms seems likely to be difficult both with regard to experiment and theory.

3. The old theoretical approaches of salt and water biophysics based on dilute solutions, pumps, and channels are not valid and have been replaced by three new theoretical approaches, which are (A) the association-induction hypothesis of Ling,[10,30] (B) the ion exchanger resin and cytotonus theory of Damadian,[31-35] and (C) the solid state physical theory of Cope,[18-21] All three approaches are based on the physico-chemical realities of associated cations and structured water. The three approaches probably overlap and are equivalent to a considerable degree. They use different approximations to reality, which lead to different methods of mathematical analysis. The association-induction method uses statistical-mechanical analysis, which can be highly exact and all-inclusive, but is so complicated mathematically that it is difficult to obtain equations that are in a form simple enough for experimental verification. The ion exchange resin theory is based on thermodynamics and electrostatic theory, which leads to simpler mathematics, but is probably not suitable for handling cooperative interactions between association sites. The solid state theory is quite simple mathematically and has yielded simple predictions regarding cation leakage from cells, which have been tested experimentally, but it is probably too simple to deal with the more complicated aspects of cation transport and excitability.

4. The more complex applications of the new picture of salt and

water biophysics now need to be developed. These include excitability (to replace Hodgkin-Huxley theory), and cation transport across multicellular membranes, e.g. frog skin.[39]

5. The new picture of salt and water biophysics now stands ready to be applied to medical diagnosis and therapy. Past medical salt and water therapy has been entirely empirical. This was necessary because the old picture of salt and water metabolism was not based on physico-chemical reality, and therefore had no predictive value. The old picture of salt and water metabolism has never to my knowledge led to any useful medical results. The new picture (specifically the ion exchange resin concept of Damadian[32-34]) has already led to the discovery of a fast and accurate method for cancer diagnosis in tissue biopsies by NMR[28-29] which is being widely studied, and has even been used by Damadian[40] to show a cross-sectional image of a cancer in an intact animal. Applications to other diseases await the interested investigator.

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This project is intended to provide improved understanding of salt and water metabolism and of solid state physical electron transport in cells, in order to improve medical treatment of shock and of other salt and water disease problems, to facilitate the use of electromagnetic fields in healing and to understand their harmful effects. Comprehensive yet elementary summaries of the recent revolution in salt and water biophysics have been written and are attached. (Appendices A and B). The Weber-Fechner law of physiological and psychological response to stimuli is shown to be a consequence of structured water and associated cations in cells. Nerve conduction and muscle contraction are suggested to involve cooperative interactions of the cation association site and structured water system. Electron interactions with structured water leading to superconduction in living systems are shown to be a possible mechanism for non-thermal effects of microwaves on biological systems.

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